Oral Magnesium Supplementation in Insulin-requiring Type 2 Diabetic Patients

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Oral magnesium (Mg) supplementation can improve insulin sensitivity and secretion in patients with Type 2 diabetes mellitus (DM). We studied the effect of Mg supplementation on glycaemic control, blood pressure, and plasma lipids in insulin-requiring patients with Type 2 DM. Fifty moderately controlled patients were randomized to 15 mmol Mg or placebo daily for 3 months. Plasma Mg, glucose, HbA_{1c}, lipids, erythrocyte Mg, Mg and glucose concentrations in 24-h urine, and systolic and diastolic pressure were measured before and after 3 months treatment. Plasma Mg concentration was higher after supplementation than after placebo (0.82 ± 0.07 vs 0.78 ± 0.08 mmol l^{-1}, $p < 0.05$), as was Mg excretion (5.5 ± 1.9 vs 3.7 ± 1.4 mmol $24\ h^{-1}$, $p = 0.004$) but erythrocyte Mg concentrations were similar. No significant differences were found in glycaemic control (glucose: 10.7 ± 3.8 vs 11.6 ± 6.2 mmol l^{-1}, $p = 0.8$; HbA_{1c}: 8.9 ± 1.6 vs $9.1 \pm 1.2\%$, $p = 0.8$), lipids or blood pressure. On-treatment analysis (34 patients: 18 on Mg, 16 on placebo) yielded similar results. An increase in plasma Mg concentration irrespective of medication was associated with a tendency to a decrease in diastolic pressure (increased plasma Mg vs no increase: -4.0 ± 10.1 vs $+2.5 \pm 12.0$ mmHg, $p = 0.059$). Three months' oral Mg supplementation of insulin-requiring patients with Type 2 DM increased plasma Mg concentration and urinary Mg excretion but had no effect on glycaemic control or plasma lipid concentrations.

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Introduction

Patients with Type 2 (non-insulin-dependent) diabetes mellitus (Type 2 DM) have slightly lower plasma magnesium concentrations compared with non-diabetic subjects, although these do not usually fall into the hypomagnesaemic range.[1–3] The low levels are attributed to glucosuria-related increased renal magnesium loss.[2,4] Hypomagnesaemia has been associated with decreased glucose disposal both in patients with Type 2 DM and in non-diabetic subjects.[5] Paolisso *et al*. have shown that oral magnesium supplementation in patients with Type 2 DM and mildly decreased plasma magnesium levels improves insulin sensitivity and secretion.[6–8]

Despite these beneficial effects on insulin secretion and sensitivity, the effect of magnesium supplementation on indices of glycaemic control in patients with Type 2 DM are less evident. In both studies by Paolisso *et al*., performed in patients not on insulin, a decrease in fasting plasma glucose concentration was reported.[6,7] Nadler *et al*. showed in a non-placebo-controlled study that HbA_{1c} fell 1.3 % after 3 months supplementation in patients on oral medication or insulin.[9] In contrast, Gullestad *et al*. failed to observe a beneficial effect on glycaemic control in a group of insulin-treated and non-insulin-treated patients.[10] In all these studies, mean plasma magnesium concentration was significantly lower in patients than in healthy controls, but patients were not necessarily hypomagnesaemic. Eibl *et al*. also could not demonstrate a beneficial effect in hypomagnesaemic patients treated with oral medication.[11]

These conflicting reports on the effect of magnesium supplementation on glycaemic control together with the demonstration of beneficial effects on insulin sensitivity and secretion in patients with mildly lowered plasma magnesium levels, but not necessarily hypomagnesaemia, has led to the present study. We performed a double-blind, placebo-controlled study to assess the effect of oral magnesium supplementation on glycaemic control in patients with insulin-requiring Type 2 DM without optimal glycaemic control but without necessarily hypomagnesaemia.

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Subjects, Materials, and Methods

Patients

Fifty patients with Type 2 DM participated. The inclusion criteria were: age at clinical onset of diabetes >40 years, initial (>1 year) adequate control with oral medication and/or presence of endogenous insulin secretion as evidenced by basal plasma C-peptide levels >0.10 nmol l^{-1}, and use of insulin for at least 6 months. Exclusion criteria were: age >80 years, use of magnesium-containing compounds within the last 3 months, use of potassium-sparing diuretics, renal impairment (plasma creatinine level >150 μmol l^{-1}) or gastrointestinal disease. All patients gave written informed consent. The protocol was approved by the Ethics Review Board of the hospital.

Study Protocol

Blood samples were taken in the morning after an overnight fast before and after supplementation together with a 24-h urine sample. Magnesium status was assessed by plasma magnesium concentrations and urinary magnesium excretion, together with erythrocyte magnesium concentrations as an index of intracellular magnesium. Severe hypoglycaemic episodes were defined according to the DCCT-trial.[12]

Medication

Patients were randomized to receive 15 mmol of magnesium-aspartate-HCl (Verla-Pharm, Tutzing, Germany) or placebo. Compliance was assessed by pill-counting and was deemed satisfactory when ≥80 % of the medication had been taken. Patients were asked to continue their regular diet and not to alter their insulin regimen or co-medication.

Analytical Procedures

Plasma magnesium, calcium, glucose, cholesterol, HDL, triglyceride, and creatinine concentrations were measured with a Kodak Ectachem analyzer, and HbA_{1c} was measured by using a HPLC method (normal value: 5.5 ± 0.5 %). Erythrocyte magnesium concentration was measured according to Paolisso.[6,7] Urinary magnesium, glucose, and creatinine concentrations were determined in 24-h specimens.

Statistical Analysis

The group size required was determined on the basis of a change in HbA_{1c} as primary parameter of effect. With a power (β) of 80 %, a threshold (α) of 5 %, a standard deviation (σ) of 1.0 %, and a change (δ) in HbA_{1c} of 1.0 %, the minimal group size was 32 patients (16 patients in each group).[13] We felt it prudent to include 50 patients (25 in each group) to allow for drop outs. The results were analysed on an intention-to-treat basis and on an on-treatment basis. The effect of intervention was assessed both by comparing the parameters between the two groups after the trial and by comparing the change during the intervention between the two groups. Parameters with a normal distribution are presented as mean ± SD and parameters with a skewed distribution as the geometric mean and the 95 % confidence interval (between parenthesis). The results after intervention are tested with the Student's *t*-test, in case of skewed distribution after logarithmic transformation. Possible confounding factors (sex, age, duration of disease, duration of insulin treatment, insulin dose, use of loop diuretics, beta blocking agents, calcium antagonist, angiotensin-converting enzyme inhibitors, presence of any form of retinopathy, presence of proliferative retinopathy, and presence of macro-angiopatic complications) were accounted for in ANOVA analysis. In addition, change in plasma magnesium concentration was dichotomized into positive change (increase in plasma magnesium concentration of ≥0.01 mmol l^{-1}) or no positive change (no change or decrease in plasma magnesium), independent of trial medication. Associations between variables were tested by regression analysis and correlation coefficients were calculated. The level of significance was 0.05.

Results

The baseline characteristics of the study groups were comparable (Table 1). Plasma magnesium concentration was not related to plasma glucose or HbA_{1c} concentration at baseline but urinary magnesium and glucose excretion were correlated ($r = +0.45$, $p = 0.012$). Plasma magnesium was not associated with the plasma calcium concentration. The C-peptide level was not associated with plasma glucose, HbA_{1c}, blood pressure, plasma magnesium or calcium levels.

The effects of supplementation (intention-to-treat and on-treatment) are shown in Table 2. Sixteen patients were considered as drop-outs for the on-treatment analysis, leaving 34 patients over (18 on magnesium, 16 on placebo). The reasons for exclusion were: early cessation of the trial (5 patients; 4 because of personal circumstances unrelated to the trial, 1 because of difficulty with swallowing the medication); non-compliance (3 patients); HbA_{1c} outside the 7–11 % window at the start of trial despite HbA_{1c} being between 7 and 11 % at screening (7 patients); physician-instigated change in insulin regimen (1 patient).

After treatment a modest but statistically significant higher plasma magnesium concentration was observed in the supplementation group than in the placebo group and was associated with an increase in urinary magnesium excretion with a similar degree of glucosuria. There was no significant difference in erythrocyte magnesium concentrations. Glycaemic control was not improved

Table 1. Baseline characteristics of the supplementation group and the control group

	Supplementation group	Control group	*p*
Number of patients	25	25	
Age (yr)	63.0 ± 8.2	62.0 ± 7.3	0.7
Sex (M/F)	16/9	12/13	0.4
Duration of clinical diabetes (yr)	16.1 ± 8.1	15.1 ± 7.6	0.7
Duration of insulin treatment (yr)	4.5 (3.0–6.7)	5.4 (3.7–7.8)	0.5
Body mass index (kg m^{-2})	28.7 (26.7–30.9)	27.1 (25.4–28.9)	0.2
Waist/hip ratio	0.93 ± 0.09	0.92 ± 0.07	0.7
Loop diuretics (*n*(%))	0 (0)	3(12)	0.2
Plasma magnesium (mmol l^{-1})	0.79 ± 0.04	0.77 ± 0.08	0.6
Plasma calcium (mmol l^{-1})	2.418 ± 0.110	2.378 ± 0.116	0.2
Erythrocyte magnesium (mmol l^{-1} RBC)	2.48 ± 0.34	2.54 ± 0.34	0.6
Plasma glucose (mmol l^{-1})	11.8 ± 3.6	11.9 ± 5.7	0.8
Plasma HbA_{1c} (%)	8.65 ± 1.45	8.72 ± 1.27	0.9
Plasma cholesterol (mmol l^{-1})	6.08 ± 0.98	5.68 ± 0.92	0.14
Plasma HDL-cholesterol (mmol l^{-1})	1.28 ± 0.38	1.31 ± 0.32	0.8
Plasma triglycerides (mmol l^{-1})	1.63 (1.32–2.02)	1.56 (1.22–2.00)	0.8
Urinary magnesium excretion (mmol Mg 24 h^{-1})	3.6 ± 1.5	4.4 ± 1.9	0.2
Urinary glucose excretion (g glucose 24 h^{-1})	3.5 (1.6–12.3)	8.7 (4.4–17.5)	0.3
Systolic blood pressure (mmHg)	162.6 ± 23.3	157.4 ± 23.6	0.4
Diastolic blood pressure (mmHg)	84.0 ± 11.5	83.0 ± 14.2	0.8

Results are presented as mean ± SD in case of normal distribution and as geometric mean and 95 % confidence interval (in parentheses) in case of skewed distribution.

Table 2. Results after 3 months for the supplementation group and the control group: intention-to-treat analysis and on-treatment analysis

	Intention-to-treat		*p*	On-treatment		*p*
	Supplement group	Control group		Supplement group	Control group	
Number of patients	25	25		18	16	
Plasma magnesium (mmol l^{-1})	0.82 ± 0.07	0.78 ± 0.08	<0.05	0.81 ± 0.07	0.77 ± 0.05	0.06
Plasma calcium (mmol l^{-1})	2.405 ± 0.110	2.412 ± 0.110	0.6	2.402 ± 0.105	2.423 ± 0.105	0.4
Erythrocyte magnesium (mmol l^{-1} RBC)	2.47 ± 0.23	2.41 ± 0.33	0.5	2.38 ± 0.38	2.38 ± 0.27	0.5
Plasma glucose (mmol l^{-1})	10.7 ± 3.8	11.6 ± 6.2	0.8	10.9 ± 3.8	12.4 ± 6.5	0.7
Plasma HbA_{1c} (%)	8.9 ± 1.6	9.1 ± 1.2	0.6	9.1 ± 1.5	9.1 ± 1.1	0.9
Plasma cholesterol (mmol l^{-1})	6.57 ± 1.43	6.03 ± 1.06	0.15	6.58 ± 1.60	5.96 ± 0.95	0.2
Plasma HDL-cholesterol (mmol l^{-1})	1.32 ± 0.44	1.35 ± 0.35	0.8	1.24 ± 0.31	1.39 ± 0.41	0.2
Plasma triglycerides (mmol l^{-1})	1.57 (1.24–1.97)	1.63 (1.24–2.13)	0.8	1.61 (1.25–2.09)	1.52 (1.13–2.04)	0.7
Urinary magnesium excretion (mmol Mg 24 h^{-1})	5.5 ± 1.9	3.7 ± 1.4	0.004	5.6 ± 1.9	3.6 ± 1.5	0.003
Urinary glucose excretion (g glucose 24 h^{-1})	6.0 (1.9–18.9)	9.5 (3.3–27.7)	0.4	6.4 (1.8–23.3)	10.3 (3.2–32.9)	0.4
Systolic pressure (mmHg)	154.9 ± 20.7	147.0 ± 22.4	0.11	158.7 ± 20.0	146.9 ± 21.8	0.11
Diastolic pressure (mmHg)	83.7 ± 9.2	82.2 ± 16.8	0.2	82.9 ± 8.3	77.1 ± 8.4	0.051

Results are given as mean ± SD in case of normal distribution and as geometric mean and 95 % confidence interval (in parentheses) in case of skewed distribution.

with magnesium supplementation (Figure 1), and blood pressure or plasma lipids were not altered. Similar results were obtained when the change in glycaemic control, blood pressure or lipid concentrations during the intervention was analysed instead of the absolute value after intervention. The results were not altered after correction for possible confounders nor when the C-peptide level was taken into account with an ANOVA-analysis. No side-effects of supplementation were reported and none of the patients experienced a severe hypoglycaemic episode.

An increase in plasma magnesium concentration, irrespective of trial medication, was not related to a change in glycaemic control, plasma lipid concentrations or systolic or diastolic pressure or the change in these parameters during the study, with the exception of change in diastolic pressure (Figure 2). Diastolic pressure decreased as plasma magnesium concentration increased, but this was not statistically significant: change in diastolic pressure with increase in plasma magnesium: –4.0 ± 10.1 mm Hg vs change in diastolic pressure

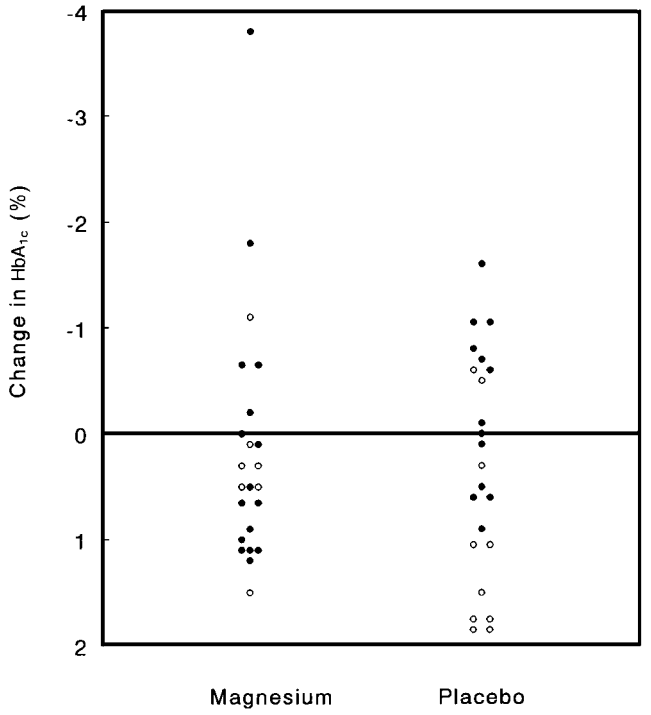

Figure 1. Change in HbA_{1c} with intervention for patients on magnesium or placebo. Solid circles represent patients with adequate compliance, open circles patients with insufficient compliance

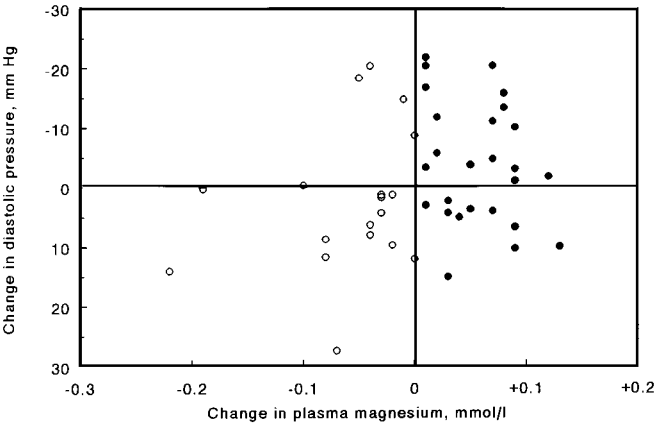

Figure 2. Change in the diastolic blood pressure in patients with a rise in plasma magnesium concentration (solid circles) and those without such a rise (open circles), irrespective of treatment with magnesium or placebo. The horizontal line denotes the zero point (no change) in the diastolic blood pressure; the vertical line denotes the zero point (no change) in the plasma magnesium (no change)

without increase in plasma magnesium: $+2.5 \pm 12.0$ mmHg, $p = 0.059$). The correlation coefficient between change in plasma magnesium and diastolic pressure was –0.25 ($p = 0.098$). No relations between changes in end parameters and a change in the plasma calcium concentration were observed.

Discussion

Three months of magnesium supplementation did not improve glycaemic control or affect plasma lipid concentrations or blood pressure in insulin-treated patients with Type 2 DM despite a small increase in the plasma magnesium level. An increase in plasma magnesium level, irrespective of treatment, was associated with a decrease in diastolic pressure, which did not achieve statistical significance.

The current study was performed in patients with insulin-requiring Type 2 DM without necessarily hypomagnesaemia. Two considerations have led to this choice. Hypomagnesaemia was not a necessary inclusion criterion because beneficial effects on insulin secretion and action have been observed in patients with mildly lowered plasma magnesium levels, but not necessarily in the hypomagnesaemic range.[6–8] In addition, the positive association between plasma magnesium concentration and glucose disposal reported by Yajnick *et al.* was observed in patients who were hypomagnesaemic or normomagnesaemic.[5] Insulin-requiring patients with Type 2 DM were chosen because these, mostly elderly, patients often have inadequate glycaemic control. Insulin is the only treatment modality and self-measurement of blood glucose levels is often less successful than in younger patients with Type 1 DM. A nutritional strategy which improves glycaemic control without major changes in the insulin regimen would be most welcome. The Clinical Practice Recommendations of the American Diabetes Association advises the measurement of plasma magnesium in high-risk patients and treatment when hypomagnesaemia is found.[14] The potential beneficial effect of increasing the plasma magnesium level within the normal range in our patients, without the necessity of intensifying insulin regimen and surveillance, led us to include non-hypomagnesaemic patients.

Erythrocyte magnesium concentrations were not low in this patient group. Low magnesium concentrations have been described in patients with non-insulin-requiring Type 2 DM,[6,7] but not in patients with Type 1 DM or insulin-requiring Type 2 DM.[15,16] Since insulin stimulates the influx of magnesium into the erythrocyte,[17,18] high circulating levels of insulin with insulin therapy may explain these normal erythrocyte magnesium levels.

Since a rise in the plasma magnesium concentration has been linked to improvement of insulin sensitivity,[5,6,8] the plasma magnesium concentration is an important issue. A modest rise in plasma magnesium was observed in the present study. The dose of magnesium supplementation that can be used is limited by the occurrence of side-effects, most notably gastrointestinal. An increase in the plasma magnesium concentration was associated with a decrease in the diastolic pressure, but this result failed to reach statistical significance. It should be remembered that we selected group size and patients on the basis of glycaemic control and not on baseline

diastolic pressure. Several studies have shown an inverse relation between daily magnesium intake and blood pressure, although none were done specifically with patients with diabetes.[19,20] The association between magnesium and blood pressure control has been linked to the role of magnesium in the regulation of intracellular cation concentrations.[21,22] In the studies by Eibl *et al*. and Gullestad *et al*. no effect of magnesium supplementation on mean blood pressure compared to placebo was observed, although they did not analyse the change in plasma magnesium and blood pressure as was done in this study.[10,11]

In conclusion, although supplementation with 15 mmol Mg orally for 3 months for insulin-requiring patients with Type 2 DM did not have an effect on glycaemic control, plasma lipids, blood pressure or erythrocyte magnesium concentrations, the potential to decrease diastolic blood pressure with an increase in the plasma magnesium concentration merits further investigation.

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